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Mortality in Young Adults Following *in Utero* and Childhood Exposure to Arsenic in Drinking Water

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CONFLICTS OF INTEREST

None declared.

ABBREVIATIONS

COPD = Chronic Obstructive Pulmonary Disease

ICD = International Classification of Diseases

ABSTRACT

Background: Beginning in 1958, the city of Antofagasta in northern Chile was exposed to high arsenic concentrations (870 μg/L) when it switched water sources. The exposure abruptly stopped in 1970 when an arsenic removal plant commenced operations. A unique exposure scenario like this—with an abrupt start, clear end and large population (125,000 in 1970) all with essentially the same exposure—is rare in environmental epidemiology. We have previously reported evidence of increased mortality from lung cancer, bronchiectasis, myocardial infarction and kidney cancer among young adults who were *in utero* or children during the high exposure period.

Objectives: We investigated all other causes of mortality in Antofagasta among young adults who were *in utero* or 18 years old or younger during the high exposure period.

Methods: We compared mortality data between Antofagasta and the rest of Chile for people aged 30-49 during the years 1989 to 2000. We estimated expected deaths from mortality rates in all of Chile, excluding Region II where Antofagasta is located, and calculated standardized mortality ratios (SMRs).

Results: New findings provide evidence of increased mortality from bladder cancer [SMR=18.1; 95% confidence interval (CI): 11.3, 27.4], laryngeal cancer (SMR=8.1; 95% CI: 3.5, 16.0), liver cancer (SMR=2.5; 95% CI: 1.6, 3.7), and chronic renal disease (SMR=2.0; 95% CI: 1.5, 2.8).

Conclusions: In combination with previously reported increased mortality from other causes of death, we conclude that arsenic in Antofagasta drinking water has resulted in the greatest increases in young adult mortality ever associated with early life environmental exposure.

INTRODUCTION

Millions of people worldwide are exposed to arsenic in their drinking water, and arsenic is a well-documented cause of many serious health effects. The International Agency for Research on Cancer has classified arsenic in drinking water as carcinogenic to humans, based on evidence it causes cancers of the skin, lung and bladder (International Agency for Research on Cancer 2004). Chronic arsenic exposure has also been shown to cause non-cancer health outcomes in multiple organs, including reproductive, cardiovascular, pulmonary, neurologic and dermal effects (National Research Council 1999, 2001). Here we present findings after assessing all causes of death following probable *in utero* and early life exposure.

The mortality data we present are from an area in northern Chile that has some unique features that make it an ideal location to study long-term outcomes from arsenic exposure. It is the driest inhabited place on earth (McKay et al. 2003), with no private wells, so everybody drank water from the only available source: the city water supply. Antofagasta obtained drinking water from rivers that flow from springs in the Andes Mountains. Before 1958, the arsenic level of the city water supply was about 90 µg/L. In 1958, a new city water supply was installed using water from the Toconce and Holajar rivers, which contained 800 and 1300 µg/L of arsenic respectively (Smith et al. 1998). With these new river sources, the average arsenic concentration in the city water supply increased dramatically to 870 µg/L. After a water treatment plant was installed in 1970, the arsenic concentration in the city water supply dropped to 110 µg/L for about ten years and was reduced further thereafter. The water supply now contains less than 10 µg/L of arsenic.

In previous studies of mortality among adults over the age of 30, we discovered increased mortality due to lung cancer and bronchiectasis (Smith et al. 2006), kidney cancer (Yuan et al. 2010) and acute myocardial infarction (Yuan et al. 2007) among residents born during or shortly before the high exposure period. We therefore decided to extend our analysis to assess mortality from all causes of death among young adults who were born during or before the high exposure period.

METHODS

We have previously reported the methods used for mortality studies in northern Chile (Smith et al. 2006; Yuan et al. 2010). In brief, we obtained computerized mortality data for 1989–2000 from the Ministry of Health for all 13 regions of Chile. Deaths were divided into two groups: residents of Antofagasta and neighboring Mejillones (cities located in Region II of Chile that have the same water source), and residents in all Regions of Chile other than Region II. Antofagasta is very much larger than Mejillones, so for brevity, when we refer to Antofagasta we mean Antofagasta and Mejillones combined. The first year, 1989, was selected because it is the first year for which deaths in Antofagasta were reported separately from the rest of Region II. Other parts of Region II also had arsenic in drinking water, although to a lesser extent than Antofagasta. Outside of Region II, the rest of Chile has not been exposed to high levels of arsenic in drinking water. With rare exceptions, arsenic concentrations in water sources outside of Region II have been below 10 μg/L. In a 1984 nationwide survey of 2,000 people, average urine arsenic concentrations were 14 μg/L (Venturino 1991). This is similar to average levels found in the general US population of 16.7 μg/L and indicates very low arsenic concentrations in

drinking water (Steinmaus et al. 2009). We also obtained survey and census data comparing variables such as smoking, diet, and socioeconomic status from Antofagasta and the rest of Chile, to evaluate potential confounding from these factors.

In this paper, we focus on deaths during the years 1989-2000 among those 30-49 years of age. People in this age range from Antofagasta would have been *in utero*, children, or adolescents (up to age 18 years) during at least part of the high exposure period of 1958-70. The referent population was young adults aged 30-49 during 1989 – 2000 from all of Chile other than Region II. Two birth cohorts were defined for this investigation: births during 1958–1970 (probable *in utero* and childhood exposure if born in Antofagasta), and births during 1940–1957 (probable childhood, but not *in utero*, exposure if born in Antofagasta).

Causes of death were coded according to the *International Classification of Diseases, 9th Revision* (ICD-9; World Health Organization 1978). The Ministry of Health coded causes of death for 1989-1998 using ICD-9 and for 1999-2000 according to the 10th revision (ICD-10). We converted all ICD-10 codes into ICD-9 codes. In our initial analysis, we noticed that several causes of death listed under ICD codes 580-589 (genitourinary) exhibited elevated SMRs. The excess deaths were limited to chronic renal failure (ICD code 585), renal failure unspecified (ICD 586), chronic glomerulonephritis (ICD 582) and renal sclerosis (ICD 587). Each of these causes of death relates to chronic renal disease and renal failure, and we therefore grouped them together and present the results as mortality from chronic renal disease.

We obtained annual estimates of the population living in Antofagasta in Region II, and for the rest of Chile excluding Region II, for 1989–2000, from the National Institute of Statistics (Instituto Nacional de Estadísticas) stratified by age and sex. We calculated standardized mortality ratios (SMRs) for deaths among those aged 30–49, using 10-year age groups (30–39 and 40–49 years) for age standardization. We calculated tests of significance and confidence intervals (95% CIs) based on the Poisson distribution (Selvin 1995). In view of the clear direction of the *a priori* hypotheses for arsenic causing increased risks for both malignant and nonmalignant diseases, we present one-tailed tests of statistical significance. We tested for effect modification by age group (comparing 30–39 and 40–49 year age groups) and effect modification by gender, using Poisson regression interaction terms with two-tailed tests . We also tested for effect modification by birth period, comparing mortality for those born in 1940-1949 with those born 1950-1957, but we report results for both periods combined, as there were no significant differences by birth period for any outcome ($p>0.05$). Mortality at ages 30-49 among those born in 1940-1957, who would have experienced at least part of their exposure ≤ 18 years of age, was compared to mortality among those born during 1958-1970, most of whom would have been exposed *in utero* if born in Antofagasta.

RESULTS

Based on a 1990 survey of Chile cities that included Antofagasta (CASEN 1990) the prevalence of smoking in 1990 was comparable between Antofagasta and the rest of Chile (Table 1). Demographic characteristics for Region II from the 2002 Census (Instituto Nacional de Estadisticas Chile 2002)are similar for Region II and Chile as a whole, including percent of

urban population (98% and 87%) and percent of medically certified death certificates (90% and 86%). Diet and other health risk factors collected in studies of stratified random population census samples conducted in 2003 and 2009 (Gobierno de Chile 2003), including obesity, blood cholesterol, glucose and hypertension, were also similar between the comparison populations.

We first estimated SMRs comparing specific causes of death among adults aged 30-49 born in Antofagasta during 1940-1970 (both genders combined) to the rest of Chile (data not shown). There was no increased mortality from infectious and parasitic diseases (SMR=1.0; 95% CI 0.8, 1.3 for ICD-9 codes 001-139), endocrine and nutritional diseases (SMR=1.2, CI 0.7, 1.8 for ICD-9 codes 240-279), diseases of the respiratory system (SMR=1.1, CI 0.9, 1.3 for ICD-9 codes 460-519), or diseases of the digestive system (SMR=0.8, CI 0.7, 0.9 for ICD-9 codes 520-579). Mortality was increased for all cancers combined (SMR=1.7, CI 1.6-1.9, $p<0.001$ for ICD-9 codes 140-239), deaths from circulatory diseases (SMR=1.7, CI 1.5, 2.0, $p<0.001$ for ICD-9 codes 390-459), and diseases of the genitourinary system (SMR=2.0, CI 1.5, 2.8, $p<0.001$ for ICD-9 codes 580-629).

Table 2 presents the SMRs for selected causes of death in Antofagasta for males and females in the age range 30-49 for the years 1989-2000, with the expected numbers estimated from the rest of Chile (excluding Region II, where Antofagasta is located), as described above. The “all other cancers” category comprises all cancers other than bladder, larynx and liver cancers, and also excluding lung and kidney cancers which we have previously shown to be associated with early life arsenic exposure (Smith et al. 2006; Yuan et al. 2010). Mortality for all cancers combined was increased for males born during 1940 – 1957, most of whom would have experienced at

least some exposure before age 18 years (SMR=2.1; CI: 1.9, 2.4; p<0.001), and for those born during the high exposure period (1958 – 1970), most of whom would have experienced both *in utero* and childhood exposure (SMR=2.2; CI: 1.7-2.8; p<0.001). Mortality from all cancers combined was also increased among females, but to a lesser extent than in men (SMR=1.4; 95% CI: 1.2, 1.6 and SMR=1.4; 95% CI: 1.1, 1.8 for those born in 1940 – 1957 and 1958 – 1970, respectively).

Mortality from bladder cancer was greatly increased in men and women (Table 2), particularly among those born during the high exposure period with probable exposure *in utero* (SMR=65.7; 95% CI: 24.1, 143 and SMR=43.0; 95% CI: 8.9, 126; p = 0.01 for interaction between birth periods 1940-1957 and 1958-1970 for men and women combined, adjusted for gender). Increases in liver cancer mortality were also more pronounced for those born during 1958-1970 (male SMR=5.9; 95% CI: 1.9, 13.; female SMR= 4.7; 95% CI: 1.3, 12.; p=0.04 for interaction by birth period among men and women combined). Mortality from laryngeal cancer was increased among men born in 1940 – 1957, before the high exposure period (SMR=8.9; 95% CI: 3.6, 18.3).

Among non-cancer causes of death for young adults aged 30-49 we observed evidence of increased mortality from chronic renal disease, with SMRs in the range of 1.9-2.5 for men and women born during or before the high exposure period (Table 2).

When data for both time periods were combined, there were no significant differences in SMRs by sex for outcomes evaluated for the first time in the present study, or for outcomes evaluated

previously using SMRs for different time periods or separately for men and women [lung cancer, bronchiectasis, and other COPD (Smith et al. 2006), acute myocardial infarction (Yuan et al. 2007), kidney cancer (Yuan et al. 2010) (Figure 1)]. The highest combined SMRs were for bladder cancer (SMR=18.1; 95% CI: 11.3, 27.4) and bronchiectasis (SMR=18.4; 95% CI: 10.3, 30.4).

DISCUSSION

We found increases in mortality from several different causes of death in the age range 30-49. We have previously reported increases in lung cancer and bronchiectasis in Chile following early life arsenic exposure (Smith et al. 2006), and increases in bronchiectasis in India after adult exposure (Guha Mazumder et al. 2005). We also previously reported increases in mortality after early life exposure from kidney cancer in Antofagasta (Yuan et al. 2010), and myocardial infarction (Yuan et al. 2007). Bladder cancer SMRs from the present analysis for adults aged 30-49 who were born during the high exposure period (males SMR=65.7; 95% CI: 24.1, 143, females SMR=43.0; 95% CI: 8.9, 126) are 5-10 times higher than the SMRs we reported previously for all ages combined regardless of age of exposure (males 6.0, females 8.2) (Smith et al. 1998).

The associations between early life exposure to arsenic and laryngeal cancer mortality are the first evidence we know of suggesting that this cancer might be related to arsenic exposure, though the number of laryngeal cancer deaths was very small and the association was only evident among men.

The findings concerning chronic renal disease mortality were unexpected, although one study in Taiwan reported a relationship between arsenic and mortality from renal diseases but the study did not specifically investigate early life exposure (Chiu and Yang 2005). In the Taiwan study area, residents had consumed arsenic-contaminated well water with a median concentration of 780 μg/L, and had renal disease mortality rates 50% higher than unexposed populations. That renal disease might relate to arsenic in water is plausible, since arsenic is excreted through the kidney and is a probable cause of kidney cancer (National Research Council 2001; Yuan et al. 2010) .

Adult liver cancer has been linked to arsenic exposure, primarily in studies in Taiwan (Chiu et al. 2004). Our previous study showed little evidence of increased mortality from liver cancer in Region II of Chile in adults, but that study did not evaluate early life exposure (Smith et al. 1998). However, in a subsequent analysis of childhood cancers, liver cancer mortality in children ages 10-19 was increased in Region II compared with Region V males relative risk (RR)= 8.9; 95% CI: 1.7, 45.8; P=0.009, females RR=14.1; 95% CI: 1.6, 126; P=0.018) (Liaw et al. 2008). The data we present here, on the other hand, are to our knowledge the first to link early life arsenic exposure to liver cancer mortality in young adults.

A major strength of this study is the large size of the exposed population: there were over 125,000 residents in Antofagasta and Mejillones in 1970, exposed to arsenic water concentrations of 870 μg/L, including approximately 60,000 children with early life exposure during the high exposure period. The largest cohort study on arsenic conducted in Taiwan involved only 698 subjects aged ≥ 40 exposed to arsenic concentrations of more than 300 μg/L

(Chiou et al. 2001). Recently published cohort studies in Bangladesh involved 10,431 subjects exposed above 300 μg/L at ≥15 years in the largest study (Sohel et al. 2009) and 2889 subjects exposed above 150 μg/L at ≥ 18 years in the second largest In addition, the populations studied in Taiwan, India and Bangladesh received their water from a large number of small town or domestic wells with wide variations in arsenic concentrations, even between closely located wells (Guha Mazumder et al. 1998; Van Geen et al. 2002), making it extremely difficult to accurately estimate early life exposure decades ago.

One potential weakness of this study is that it is ecological, comparing Antofagasta with the rest of Chile. However, this study does not have the usual problems associated with what is sometimes termed the "ecologic fallacy" (Morgenstern 1995), since there was only one source of drinking water with a known concentration of arsenic in Antofagasta, and we can therefore be confident that virtually everyone who lived in Antofagasta during the high exposure period was indeed exposed. Migration into and out of the study area could also introduce bias, but people migrating from Antofagasta to elsewhere in Chile would constitute a very small proportion of the total Chilean population, and any resulting bias would tend to reduce relative mortality estimates for Antofagasta since deaths that may have been a consequence of exposure would not be counted if they occurred outside of Antofagasta. Migration into Antofagasta also would tend to bias estimates toward the null because these residents would be misclassified as exposed if they did not reside in Antofagasta during the high exposure period. In addition, migration within Chile is relatively uncommon: from 1965 to 2000, annual internal migration among regions of Chile was only 0.6 percent, compared with 1.2 percent in Argentina, 3.1 percent in the United Kingdom, and 6.6 percent in United States (Soto and Torche 2004).

Another potential weakness is that the study involves death certificate data. Based on Census 2002 data, in Chile, the large majority of death certificates (86%) are signed by physicians, and in Region II where Antofagasta is located, the percentage is similar (90%) to Chile as a whole (Instituto Nacional de Estadisticas Chile 2002). Also, Chile has a national health care system that services the whole country (Reichard 1996). Therefore it is unlikely that differences in diagnostic practices between Antofagasta and the rest of Chile could produce spurious differences in mortality rates.

The importance of ecological studies in causal inference concerning arsenic in drinking water was recognized in IARC Monograph 84, 2004. "For most other known human carcinogens, the major source of causal evidence arise from case-control and cohort studies, with little, if any, evidence from ecological studies. In contrast, for arsenic in drinking-water, ecological studies provide important information on causal inference, because of large exposure contrasts and limited population migration" (International Agency for Research on Cancer 2004).

There are two reasons why confounding is not a concern. The first reason involves the magnitude of the mortality rate ratios identified. Consider, for example, the SMRs for AMI mortality among Antofagasta men of 2.3 and 2.7 for births during 1940 – 1957 and 1958 – 1970, respectively, which are comparable to the AMI mortality rate ratio was 2.11 for current cigarette smokers who smoked more than 20 pack-years compared with never smokers from a large cohort study of about 140,000 men in the United States (Henderson et al. 2007). These similarities suggest that confounding by smoking would explain our SMRs only if all men in Antofagasta smoked, and

no men smoked in the rest of Chile. Similarly, confounding by smoking would not explain the estimated SMRs for lung cancer, laryngeal cancer and bladder cancer.

Confounding is also not a major concern because there is no evidence of major risk factor differences between Antofagasta and the rest of Chile (other than arsenic). For example, a survey conducted in 1990 indicated that the prevalence of smoking in Region II (27.4% in men and 16.6% in women) was similar to Chile as a whole (26.6% in men and 19.3% in women) (Marshall et al. 2007). It is also extremely unlikely for other confounding factors, including diet or exercise, to produce the magnitude of the SMRs we report. As shown in Table 1, other cardiovascular mortality risk factors, including BMI, obesity, cholesterol and hypertension, also did not differ substantially between Region II and all of Chile in 2003 (Gobierno de Chile 2003). Having given consideration to all potential sources of bias, we conclude that our study provides strong epidemiological evidence of increased mortality risks from several causes in young adults exposed to arsenic in early life.

Inorganic arsenic and its metabolites readily pass through the placenta, exposing the fetus to similar concentrations as the mother (Concha et al. 1998). Animal experiments have shown that arsenic is a transplacental carcinogen in mice that causes tumors in offspring (Tokar et al. 2011; Waalkes et al. 2007). Recent research has shown that arsenic acts epigenetically and interferes with DNA methylation (Vahter 2008). Arsenic exposure may alter DNA methylation, globally affecting the expression of multiple genes (Ren et al. 2010), which may explain why exposure to arsenic is associated with multiple disease outcomes in different organs.

We know of no childhood environmental exposure that results in comparable increases in adult mortality rates as summarized in Figure 1. Mortality from pancreatic cancer and leukemia were increased in young adults after arsenic exposure from contaminated milk powder in Japan involving exposures that were very high and resulted in acute poisoning effects (Yorifuji et al. 2010). A study of 60,182 people reported elevated lung cancer risks from childhood passive smoking, but the relative risk from "daily, many hours" of passive smoking exposure was 3.63 (95% CI: 1.19, 11.11) and there were only four cases of lung cancer in this group (Vineis et al. 2005). Other studies of passive childhood smoking have not found increased risks (Boffetta et al. 2000). A non-environmental exposure—radiation treatment of childhood cancer—causes major increases in later mortality from other cancers (excluding recurrence of the treated cancer), and from non-cancer outcomes. A recent report from the Childhood Cancer Survivor Study showed that mortality from other cancers was increased (Relative Risk [RR] =2.9; 95% CI: 2.1, 4.2), and mortality from cardiac causes (RR=3.3; 95% CI: 2.0, 5.5) and "other" causes (RR= 2.0; 95% CI: 1.3, 3.1) were also increased (Mertens et al. 2008). Increased cancer mortality has also been demonstrated in atomic bomb survivors exposed *in utero* or as young children (Preston et al. 2008). Leaving aside these fairly rare and specific high-dose radiation exposure scenarios, our findings suggest that early life exposure to arsenic in drinking water causes greater increases in mortality in young adults than those attributable to any other early life environmental exposure.

CONCLUSIONS

To our knowledge, this is the first investigation of all causes of death in young adults following early life exposure to arsenic in drinking water. We identified pronounced increases in mortality for water arsenic concentrations around 870 µg/L, including increased mortality from cancers of

the bladder, larynx and liver and from renal diseases associated with chronic renal failure. In combination with the previously reported increased mortality from other causes, the magnitude and extent of the increased mortality we have identified are without precedent for any early life environmental exposure. Our findings need to be confirmed in other populations, but they add strong support for efforts to reduce population exposure to arsenic in drinking water, particularly during pregnancy and childhood.

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Table 1. Comparing smoking data, demographic variables and risk factors from a national random sample between Region II of Chile (of which Antofagasta constitutes more than half the total population), with all of Chile.

Variables	Region II	All of Chile
Smoking[a]		
% Non-smokers	78.0	77.5
% Moderate smokers*	21.0	21.1
% Heavy smokers**	1.0	1.2
Men smokers	27.4	26.6
Women smokers	16.6	19.3
Demographic Variables[b]		
% Urban	98	87
% Catholic	72	70
% Literate	98	97
% Pre-basic education	4	4
% University/prof. education	17	14
% Death certificates certified by physician	90	86
Medical Risk Factors[c]		
Average BMI (kg/cm^2)	27.6	26.8
Obese (BMI > 30)	19.2%	21.9%
Morbid obesity (BMI > 40)	2.8%	1.3%
Average HDL (mg/dl)	34.2	44.6
Average LDL (mg/dl)	105.0	115.4
Hypertension > 140/90	28.9%	33.5%
Average total cholesterol (mg/dl)	174.0	186.0
Average serum glucose (mg/dl)	85.8	92.9
Diabetes	3.2%	4.2%
Regular exercise	13.8%	9.2%
Dietary Risk Factors in National Survey[d]		
Gram alcohol consumed/day	41.5	55.6
Grams fruit/vegetables per day	174.0	186.0
Salt consumption/day (gram)	173.8	185.8

* > 0 to 1 pack per day
** > 1 pack per day
[a] Data from survey conducted in 1990, Ministerio de Planificación y Coordinación Nacional República de Chile llla, Encuesta CASEN 1990
[b] Data from the Chile national census conducted in 2002, http://www.ine.cl/cd2002/index.php.
[c] Data from survey conducted in 2003: Gobierno de Chile, Ministerio de salud. Resultados 1 encuesta de salud, Chile 2003, http://epi.minsal.cl/epi/html/invest/ENS/InformeFinalENS.pdf
[d] Data from Encuesta Nacional de Salud Chile 2009-2010, http://www.minsal.gob.cl/portal/url/item/bcb03d7bc28b64dfe040010165012d23.pdf

Table 2. Observed (O) and expected (E) deaths and standardized mortality ratios (SMRs) for males and females aged 30-49 for years 1989-2000 in Antofagasta[a] for those born in 1940-57 and those born during the high exposure period (1958-70).

		Born 1940-57					Born 1958-70					Interaction
Cancers	Sex	O	E	SMR	CI	p-value*	O	E	SMR	CI	P-value	p-value**
All Cancer	Male	226	105.3	2.1	1.9, 2.4	<0.001	69	30.8	2.2	1.7, 2.8	<0.001	
	Female	219	154.5	1.4	1.2, 1.6	<0.001	59	41.3	1.4	1.1, 1.8	<0.01	0.83
Bladder Cancer	Male	11	0.8	13.7	6.8, 24.5	<0.001	6	0.1	65.7	24.1, 143	<0.001	
	Female	2	0.3	7.9	1.0, 28.6	0.03	3	0.1	43.0	8.9, 126	<0.001	0.01
Larynx Cancer	Male	7	0.8	8.9	3.6, 18.3	<0.001	1	0.0	27.4	0.7, 153	0.04	
	Female	0	0.1	--	--	--	0	0.0	--	--	--	0.53
Liver Cancer	Male	10	4.1	2.4	1.2, 4.4	0.01	5	0.9	5.9	1.9, 13.7	<0.01	
	Female	6	4.1	1.5	0.5, 3.2	0.23	4	0.9	4.7	1.3, 12.0	0.01	0.04
All Other Cancers[b]	Male	79	82.9	1.0	0.8, 1.2	0.64	41	27.7	1.5	1.1, 2.0	0.01	
	Female	174	142.1	1.2	1.0, 1.4	<0.01	48	39.0	1.2	0.9, 1.6	0.09	0.36
Chronic Renal Disease[c]	Male	14	7.5	1.9	1.0, 3.1	0.02	6	2.7	2.3	0.8, 4.9	0.05	
	Female	14	7.1	2.0	1.1, 3.3	0.02	6	2.4	2.5	0.9, 5.4	0.04	0.71
All Other Non-Cancer Deaths Minus Injuries[d]	Male	310	367.7	0.8	0.8, 0.9	0.99	110	128	0.9	0.7, 1.0	0.94	
	Female	187	178.3	1.0	0.9, 1.2	0.27	89	61.8	1.4	1.2, 1.8	<0.01	0.33

* One-sided p-value

**Two-sided p-value. Test for interaction between birth periods 1940-1957 and 1958-1970 adjusted for gender

[a] All data presented for Antofagasta include neighboring Mejillones, which had the same water sources

[b] "All Other Cancers" category comprises all cancers except bladder, larynx, liver, lung and kidney; we have previously shown lung and kidney cancers to be associated with early life arsenic exposure

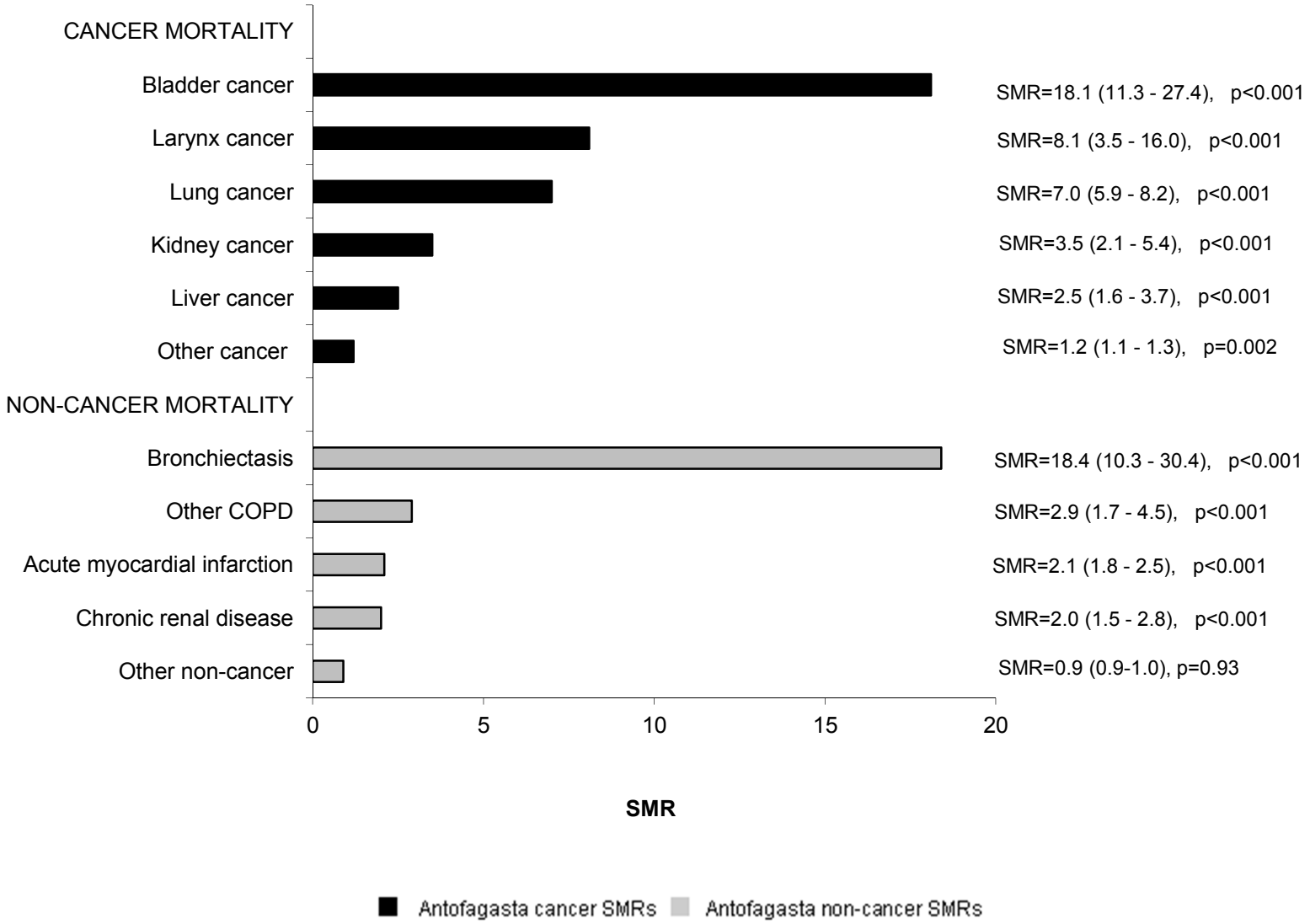
[c] ICD codes 580-589

[d] "All Other Non-Cancer Deaths Minus Injuries" comprises all non-cancer deaths except injuries, acute myocardial infarction, bronchiectasis, and other chronic obstructive pulmonary diseases; we have previously shown the last 3 diseases to be associated with early life arsenic exposure

Figure Legend

Figure 1. Summary of standardized mortality ratios (SMRs) for ages 30-49, males and females pooled, and combining those born before and during the high exposure period (Smith et al. 2006; Yuan et al. 2007; Yuan et al. 2010).

Figure 1.


CANCER MORTALITY
Bladder cancer
Larynx cancer
Lung cancer
Kidney cancer
Liver cancer
Other cancer
NON-CANCER MORTALITY
Bronchiectasis
Other COPD
Acute myocardial infarction
Chronic renal disease
Other non-cancer
SMR=18.1 (11.3 - 27.4), p<0.001
SMR=8.1 (3.5 - 16.0), p<0.001
SMR=7.0 (5.9 - 8.2), p<0.001
SMR=3.5 (2.1 - 5.4), p<0.001
SMR=2.5 (1.6 - 3.7), p<0.001
SMR=1.2 (1.1 - 1.3), p=0.002
SMR=18.4 (10.3 - 30.4), p<0.001
SMR=2.9 (1.7 - 4.5), p<0.001
SMR=2.1 (1.8 - 2.5), p<0.001
SMR=2.0 (1.5 - 2.8), p<0.001
SMR=0.9 (0.9-1.0), p=0.93
0
5
10
15
20
SMR
Antofagasta cancer SMRs
Antofagasta non-cancer SMRs